

What is claimed is:

CLAIMS

1. A method for enhancing the bioavailability of a bioactive agent *in vivo* comprising (i) administering said bioactive agent to a patient, (ii) administering a vesicle composition comprising, in an aqueous carrier, a gas or gaseous precursor and vesicles comprising lipids, proteins or polymers to the patient, and (iii) applying ultrasonic energy to the patient in an amount sufficient to produce cavitation of said vesicles, wherein said vesicle composition is administered to said patient at a rate which comprises continuous infusion.
2. A method according to Claim 1 wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.
3. A method according to Claim 1, wherein said bioactive agent and said vesicle composition are administered to said patient substantially simultaneously.
4. A method according to Claim 1, further comprising imaging said patient using diagnostic ultrasound imaging.
5. A method according to Claim 1 wherein said vesicles comprise lipids.
6. A method according to Claim 5 wherein said vesicle composition comprises vesicles selected from the group consisting of micelles and liposomes.
7. A method according to Claim 5 wherein said lipids comprise phospholipids.

8. A method according to Claim 7 wherein said phospholipids are selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid.

9. A method according to Claim 8 wherein said phosphatidylcholine is  
5 selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

10. A method according to Claim 9 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

11. A method according to Claim 8 wherein said phosphatidylethanolamine  
10 is selected from the group consisting of dipalmitoylphosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

12. A method according to Claim 11 wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

13. A method according to Claim 8 wherein said phosphatidic acid  
15 comprises dipalmitoylphosphatidic acid.

14. A method according to Claim 5 wherein said lipid further comprises a  
polymer.

15. A method according to Claim 14 wherein said polymer comprises a  
20 hydrophilic polymer.

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16. A method according to Claim 15 wherein said hydrophilic polymer comprises polyethylene glycol.

17. A method according to Claim 1 wherein said vesicles comprise proteins.

5 18. A method according to Claim 17 wherein said proteins comprise albumin.

19. A method according to Claim 1 wherein said vesicles comprise polymers.

20. A method according to Claim 19 wherein said polymers comprise  
10 synthetic polymers or copolymers which are prepared from monomers selected from the group consisting of poly-lactic acid, poly-lactide, poly-lactide co-glycolide, acrylic acid, methacrylic acid, ethyleneimine, crotonic acid, acrylamide, ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate, lactic acid, glycolic acid,  $\epsilon$ -caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkylacrylates, siloxane, dimethylsiloxane, ethylene  
15 oxide, ethylene glycol, hydroxyalkylmethacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-aminobenzylstyrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates and 2-methacryloyloxytrimethyl-ammonium chloride.

20 21. A method according to Claim 19 wherein said polymers comprise synthetic polymers or copolymers selected from the group consisting of polyacrylic acid, polyethyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, poly( $\epsilon$ -caprolactone), epoxy resin, poly(ethylene

oxide), poly(ethylene glycol), polyamide, polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-polymethylmethacrylate and polystyrene-polyacrylonitrile.

22. A method according to Claim 19 wherein said polymers comprise polyvinylidene-polyacrylonitrile copolymer.

5                    23.     A method according to Claim 1 wherein said gas comprises a fluorinated gas.

24. A method according to Claim 23 wherein said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride.

25. A method according to Claim 24 wherein said fluorinated gas  
10 comprises a perfluorocarbon.

26. A method according to Claim 25 wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

27. A method according to Claim 1 wherein said gaseous precursor has a boiling point of greater than about 37°C.

28. A method according to Claim 27 wherein said gaseous precursor comprises a fluorinated compound.

29. A method according to Claim 28 wherein said fluorinated compound comprises a perfluorocarbon.

30. A method according to Claim 29 wherein said perfluorocarbon is selected from the group consisting of perfluoropentane and perfluorohexane.

31. A method according to Claim 1 wherein said vesicle composition is administered to the patient at a rate of from about  $1 \times 10^6$  to less than about  $8 \times 10^6$  vesicles/Kg-sec.

32. A method according to Claim 31 wherein said vesicle composition is administered at a rate of from about  $1 \times 10^6$  to about  $7 \times 10^6$  vesicles/Kg-sec.

33. A method according to Claim 32 wherein said vesicle composition is administered at a rate of from about  $1.5 \times 10^6$  to about  $6 \times 10^6$  vesicles/Kg-sec.

34. A method according to Claim 33 wherein said vesicle composition is administered at a rate of from about  $2 \times 10^6$  to about  $5.5 \times 10^6$  vesicles/Kg-sec.

35. A method according to Claim 34 wherein said vesicle composition is administered at a rate of from about  $2.5 \times 10^6$  to about  $5 \times 10^6$  vesicles/Kg-sec.

36. A method according to Claim 35 wherein said vesicle composition is administered at a rate of from about  $3 \times 10^6$  to about  $4.5 \times 10^6$  vesicles/Kg-sec.

37. A method according to Claim 2 wherein said vesicle composition is administered to the patient at a rate of from about  $1 \times 10^{-7}$  to about  $3 \times 10^{-3}$  cc gas/Kg-sec.

38. A method according to Claim 37 wherein said vesicle composition is administered at a rate of from about  $3 \times 10^{-6}$  to about  $3 \times 10^{-3}$  cc gas/Kg-sec.

39. A method according to Claim 38 wherein said vesicle composition is administered at a rate of from about  $4 \times 10^{-6}$  to about  $2 \times 10^{-3}$  cc gas/Kg-sec.

40. A method according to Claim 39 wherein said vesicle composition is administered at a rate of from about  $8 \times 10^{-6}$  to about  $2 \times 10^{-3}$  cc gas/Kg-sec.

5            41.     A method according to Claim 40 wherein said vesicle composition is administered at a rate of from about  $1 \times 10^{-5}$  to about  $1 \times 10^{-3}$  cc gas/kg-sec.

42. A method according to Claim 41 wherein said vesicle composition is administered at a rate of from about  $4 \times 10^{-5}$  to about  $1 \times 10^{-3}$  cc gas/Kg-sec.

43. A method according to Claim 42 wherein said vesicle composition is  
10 administered at a rate of from about  $8 \times 10^{-5}$  to less than about  $1 \times 10^{-3}$  cc gas/kg-sec.

44. A method according to Claim 43 wherein said vesicle composition is administered at a rate of from about  $1 \times 10^{-4}$  to about  $9 \times 10^{-4}$  cc gas/Kg-sec.

45. A method according to Claim 1 wherein said bioactive agent is selected from the group consisting of a diagnostic agent, genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, a thrombolytic agent, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

46. A method according to Claim 45 wherein said bioactive agent comprises  
20 an anti-neoplastic agent.

47. A method according to Claim 46 wherein said bioactive agent comprises paclitxel.

48. The method of Claim 45 wherein said bioactive agent comprises genetic material selected from the group consisting of a nucleic acid, RNA, DNA, recombinant RNA, recombinant DNA, antisense RNA, antisense DNA, hammerhead RNA, a ribozyme, a hammerhead ribozyme, an antigene nucleic acid, a ribooligonucleotide, a deoxyribooligonucleotide, an antisense ribooligonucleotide, and an antisense deoxyribooligonucleotide.

49. A method of enhancing the delivery of a bioactive agent in tissue *in vivo* comprising (i) administering said bioactive agent to a patient, (ii) administering an acoustically active composition to said patient, and (iii) applying ultrasonic energy to said tissue in an amount sufficient to activate said acoustically active composition, wherein said acoustically active composition is administered to said patient at a rate which comprises continuous infusion.

50. A method according to Claim 49 wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

51. A method according to Claim 49 wherein said bioactive agent and said acoustically active composition are administered to said patient substantially simultaneously.

52. A method according to Claim 49 wherein said tissue comprises neoplastic tissue.

53. A method according to Claim 49 wherein said tissue comprises an area of reduced blood perfusion.

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54. A method according to Claim 53 wherein said area of reduced blood perfusion comprises ischemic tissue.

55. A method according to Claim 49 wherein said tissue comprises myocardium.

5 56. A method according to Claim 49 wherein said tissue comprises glandular tissue.

57. A method according to Claim 56 wherein said glandular tissue comprises the prostate gland.

10 58. A method according to Claim 49 further comprising imaging said tissue using diagnostic ultrasound imaging.

59. A method according to Claim 49 wherein said bioactive agent comprises an agent selected from the group consisting of a diagnostic agent, genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, a thrombolytic agent, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

15 60. A method according to Claim 49 wherein said bioactive agent comprises an anti-neoplastic agent.

20 61. A method according to Claim 60 wherein said bioactive agent comprises paclitaxel.

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62. A method according to Claim 58 wherein the bioactive agent comprises genetic material selected from the group consisting of a nucleic acid, RNA, DNA, recombinant RNA, recombinant DNA, antisense RNA, antisense DNA, hammerhead RNA, a ribozyme, a hammerhead ribozyme, an antigenic nucleic acid, a ribooligonucleotide, a deoxyribooligonucleotide, an antisense ribooligonucleotide, and an antisense deoxyribooligonucleotide.

63. A method for lysing a thrombus comprising (i) administering a thrombolytic agent to a patient; (ii) administering a vesicle composition comprising, in an aqueous carrier, a gas or gaseous precursor and vesicles comprising lipids, proteins or polymers to the patient, and (iii) applying ultrasonic energy to the thrombus in an amount sufficient to produce cavitation of said vesicles, wherein said vesicle composition is administered to said patient at a rate which comprises continuous infusion.

64. A method according to Claim 63 further comprising imaging said thrombus using diagnostic ultrasound imaging.

65. A method according to Claim 63 wherein said thrombus is in a cardiac blood vessel.

66. A method according to Claim 63 wherein said thrombolytic agent is selected from the group comprising streptokinase, urokinase, tissue plasminogen activator, alteplase, anistreplase, reteplase and saruplase.

67. A method according to Claim 66 wherein said thrombolytic agent comprises streptokinase.

68. A method according to Claim 59 wherein said acoustically active composition and bioactive agent are administered prior to said application of ultrasound energy.

69. A method according to Claim 59 wherein said acoustically active composition and bioactive agent are administered at about the same time as said application of ultrasound energy.

70. A method according to Claim 59 further comprising applying radiation energy to said tissue.

71. A method according to Claim 69 wherein said acoustically active composition and bioactive agent are administered prior to said application of radiation energy.

72. A method according to Claim 70 wherein said acoustically active composition and bioactive agent are administered at about the same time as said application of radiation energy.

73. A method according to Claim 68 wherein said acoustically active composition and bioactive agent are administered from about 1 minute to about 8 hours prior to said application of ultrasound energy.

74. A method according to Claim 71 wherein said acoustically active composition and bioactive agent are administered from about 1 minute to about 8 hours prior to said application of radiation energy.

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